



PATENT
Attorney Docket No. 401909/SKYEPHARMA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PACE et al.

Art Unit: 1616

Application No. 09/667,328

Examiner: S. S. Gollamudi

Filed: September 21, 2000

For: **SURFACE MODIFIED
PARTICULATE COMPOSITIONS OF
BIOLOGICALLY ACTIVE
SUBSTANCES**

**PENDING CLAIMS AFTER AMENDMENTS
MADE IN RESPONSE TO OFFICE ACTION DATED OCTOBER 16, 2002**

16. A composition comprising stable solid particles of a water-insoluble biologically active substance of a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

a non-aqueous hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble, and is present in an amount such that the water-insoluble biologically active substance remains insoluble in the non-aqueous hydrophobic liquid;

a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substances that provides a self-dispersing property to said composition,

wherein upon addition of said composition to a fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non aqueous hydrophobic liquid containing particles of surface stabilized water-insoluble biological substance suspended in the oily droplets of the dispersion and particles of said water-insoluble biologically active substance migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

17. The composition of claim 16 where at least one component of the non-aqueous hydrophobic liquid is selected from the group consisting of an oil derived from animal origin; a vegetable oil; a fish oil; a fish oil free fatty acid; oleic acid; linoleic acid; a poly-unsaturated fatty acid; caprylic/capric triglyceride; caprylic/capric/linoleic triglyceride; a synthetic medium chain triglyceride having a C₈₋₁₂ fatty acid chain; propylene glycol dicaprylate/caprate; linoleic acid ethyl ester; a cholesteryl fatty acid ester, a C₁₂₋₁₈ fatty acid monoglyceride, a C₁₂₋₁₈ fatty acid diglyceride, and a C₁₂₋₁₈ fatty acid triglyceride prepared from soybean oil, almond oil, sunflower oil, olive oil, and corn oil with glycerol; a pharmaceutically acceptable monohydric alcohol; a pharmaceutically acceptable alkanol; a pharmaceutically acceptable dihydric alcohol; a pharmaceutically acceptable aromatic ester; benzyl benzoate; diethyl phthalate; propyl gallate; triacetin; diacetin; monoacetin; triethyl citrate; a pharmaceutically suitable hydrophobic organic solvent; a hydrofluorocarbon in the liquid state at ambient temperature and pressure; and perflubron.

18. The composition of claim 16 where at least one surfactant component is selected from the group consisting of a natural or synthetic amphiphilic agent; a phospholipid; a nonionic surfactant; a polyoxyethylene fatty alcohol ether; a sorbitan fatty acid ester; a polyoxyethylene sorbitan fatty acid ester; glycerol triacetate; triacetin; a polyethylene glycol; cetyl alcohol; cetostearyl alcohol; stearyl alcohol; a poloxamer; a polaxamine; a polyoxethylene castor oil derivative; vitamin E; D-alpha-tocopheryl polyethylene glycol 1000 succinate; vitamin E TPGS; a PEG glyceryl fatty acid ester; PEG-8 glyceryl caprylate/caprate; PEG-4 glyceryl caprylate/caprate; PEG-32 glyceryl laurate; PEG-6 glyceryl mono oleate; PEG-6 glyceryl linoleate; a propylene glycol mono fatty acid ester; a propylene glycol di-fatty acid ester; propylene glycol laurate; propylene glycol caprylate/caprate; diethylene glycol monoethyl ether; transcutol; a monoglyceride; an acetylated monoglyceride; glycerol monooleate; glycerol monostearate; a mono-acetylated monoglyceride; a di-acetylated monoglyceride; monoacetin; diacetin; an anionic surfactant; a fatty acid salt; a bile salt; potassium laurate; triethanolamine stearate; sodium lauryl sulfate; an alkyl polyoxyethylene sulfate; sodium alginate; dioctyl sodium sulfosuccinate; sodium carboxymethylcellulose; calcium carboxymethylcellulose; a cationic surfactant; a pharmaceutically acceptable quaternary ammonium compound; benzalkonium chloride; cetyltrimethylammonium bromide; lauryldimethylbenzylammonium chloride; polyethylene glycol; PEG 1000; PEG 1500; and PEG 3400.

19. The composition of claim 18 in which the phospholipid is selected from the group consisting of a saturated phospholipid, an unsaturated phospholipid, a synthetic phospholipid, a natural phospholipid, and a combination thereof.
20. The composition of claim 16 where at least one hydrophilic component is selected from the group consisting of a low-molecular weight monohydric alcohol; a low-molecular weight polyhydric alcohol; ethanol; a glycol; glycerol; and a mixture thereof.
21. The composition of claim 16 in a dosage form for peroral, parenteral, transdermal, inhalation, or ophthalmic administration of said biologically active substance.
22. The composition of claim 16, wherein the biologically active substance is selected from the group consisting of an antihypertensive drug, an anticholinergic drug, a drug for treating a gastro-intestinal disorder, a hormone, an antineoplastic drug, an NSAID, an anti-fungal agent, an anti-viral agent, a cholesterol controlling agent, an immuno-suppressive peptide, and [a protein used in the treatment of diabetes.]
23. The composition of claim 16, wherein the biologically active substance is selected from the group consisting of nifedipine, ursodiol, budesonide, paclitaxel, camptothecin, a derivative of paclitaxel, a derivative of camptothecin, piroxicam, itraconazole, acyclovir, a derivative of acyclovir, fenofibrate, cyclosporine, and insulin.
24. The composition of claim 16 which is prepared for sustained or controlled delivery of the biologically active substance.
25. The composition of claim 16 where the fluid aqueous medium is selected from the group consisting of water, buffered water, phosphate buffered water, phosphate buffered saline, citrate buffered water, acetate buffered water, water buffered with pharmaceutically acceptable pH controlling agents, water containing salts, water containing sodium chloride, water containing pharmaceutically acceptable salts, water containing soluble agents for lyoprotection, water containing soluble agents for cryoprotection, water containing dextrose, water containing mannitol, water containing trehalose, water containing sucrose, water

containing sorbitol, water containing polyhydroxy-containing compounds, and a mixture thereof.

26. The composition of claim 16 where the fluid aqueous medium is selected from the group consisting of a biological fluid, blood, plasma, saliva, urine, a protein-containing solution, an aqueous suspension of a protein, lymph fluid, semen, vaginal fluid, lachrymal fluid, nasal fluid, synovial fluid, cerebral fluid, cerebralspinal fluid, amniotic fluid, pancreatic fluid, pulmonary fluid, ascites fluid, fluid from a cyst, gastric fluid, intestinal fluid, a fluid removed from a patient, a diluted biological fluid, a concentrated biological fluid, and a mixture of biological fluids from one or more patients.

27. The composition of claim 16 where the fluid aqueous medium contains one or more surface active agent.

28. The composition of claim 16 contained in a capsule of hard gelatin, or soft gelatin, or starch, which capsule dissolves in a fluid aqueous medium, and which capsule optionally comprises a pharmaceutically acceptable coating for controlling the release of the biologically active substance from said capsule in said fluid aqueous medium.

29. The composition of claim 16 contained in a tablet, which tablet optionally comprises a pharmaceutically acceptable coating for controlling the release of the biologically active substance.

30. A process for preparing a dosage form of a biologically active substance comprising adding to a fluid aqueous medium a composition comprising stable solid particles of said water-insoluble biologically active substance having a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

a non-aqueous hydrophobic liquid in which said biologically active substance is not soluble or is poorly soluble and is present in an amount such that the water-insoluble biologically active substance remains insoluble in the non-aqueous hydrophobic liquid;

a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substance that provides a self-dispersing property to said composition,

wherein upon addition of said composition to said fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non aqueous hydrophobic liquid containing particles of said surface stabilized water-insoluble biological substance suspended in the oily droplets of the dispersion and particles of said water-insoluble biologically active substance migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

31. The process of claim 30 where at least one component of the non-aqueous hydrophobic liquid is selected from the group consisting of an oil derived from animal origin; a vegetable oil; a fish oil; a fish oil free fatty acid; oleic acid; linoleic acid; a poly-unsaturated fatty acid; caprilic/capric triglyceride; caprylic/capric/linoleic triglyceride; a synthetic medium chain triglyceride having a C₈₋₁₂ fatty acid chain; propylene glycol dicaprylate/caprate; linoleic acid ethyl ester; a cholesteryl fatty acid ester, a C₁₂₋₁₈ fatty acid monoglyceride, a C₁₂₋₁₈ fatty acid diglyceride, and a C₁₂₋₁₈ fatty acid triglyceride prepared from soybean oil, almond oil, sunflower oil, olive oil, and corn oil with glycerol; a pharmaceutically acceptable monohydric alcohol; a pharmaceutically acceptable alkanol; a pharmaceutically acceptable dihydric alcohol; a pharmaceutically acceptable aromatic ester; benzyl benzoate; diethyl phthalate; propyl gallate; triacetin; diacetin, monoacetin; triethyl citrate; a pharmaceutically suitable hydrophobic organic solvent; and a hydrofluorocarbon in the liquid state at ambient temperature and pressure.

32. The process of claim 30 where at least one surfactant component is selected from the group consisting of a natural or synthetic amphiphilic agent; a phospholipid; a nonionic surfactant; a polyoxyethylene fatty alcohol ether; a sorbitan fatty acid ester; a polyoxyethylene sorbitan fatty acid ester; glycerol triacetate; a polyethylene glycol; cetyl alcohol; cetostearyl alcohol; stearyl alcohol; a poloxamer; a polaxamine; a polyoxethylene castor oil derivative; vitamin E; D-alpha-tocopheryl polyethylene glycol 1000 succinate; vitamin E TPGS; a PEG glyceryl fatty acid ester; PEG-8 glyceryl caprylate/caprate; PEG-4 glyceryl caprylate/caprate;

PEG-32 glyceryl laurate; PEG-6 glyceryl mono oleate; PEG-6 glyceryl linoleate; a propylene glycol mono fatty acid ester; a propylene glycol di-fatty acid ester; propylene glycol laurate; propylene glycol caprylate/caprate; diethylene glycol monoethyl ether; transcutol; a monoglyceride; an acetylated monoglyceride; glycerol monooleate; glycerol monostearate; a mono-acetylated monoglyceride; a di-acetylated monoglyceride; monoacetin; diacetin; an anionic surfactant; a fatty acid salt; a bile salt; potassium laurate; triethanolamine stearate; sodium lauryl sulfate; an alkyl polyoxyethylene sulfate; sodium alginate; dioctyl sodium sulfosuccinate; sodium carboxymethylcellulose; calcium carboxymethylcellulose; a cationic surfactant; a pharmaceutically acceptable quaternary ammonium compound; benzalkonium chloride; cetyltrimethylammonium bromide; lauryldimethylbenzylammonium chloride; polyethylene glycol; PEG 1000; PEG 1500; and PEG 3400.

33. The process of claim 32 in which the phospholipid is selected from the group consisting of a saturated phospholipid, an unsaturated phospholipid, a synthetic phospholipid, a natural phospholipid, and a combination thereof.

34. The process of claim 30 where at least one hydrophilic component is selected from the group consisting of a low-molecular weight monohydric alcohol; a low-molecular weight polyhydric alcohol; ethanol; a glycol; glycerol; and a mixture thereof.

35. The process of claim 30, wherein the biologically active substance is selected from the group consisting of an antihypertensive drug, an anticholinergic drug, a drug for treating a gastro-intestinal disorder, a hormone, an antineoplastic drug, an NSAID, an anti-fungal agent, an anti-viral agent, a cholesterol controlling agent, an immuno-suppressive peptide, and a protein used in the treatment of diabetes.

36. The process of claim 30, wherein the biologically active substance is selected from the group consisting of nifedipine, ursodiol, budesonide, paclitaxel, a derivative of paclitaxel, camptothecin, a derivative of camptothecin, piroxicam, itraconazole, acyclovir, a derivative of acyclovir, cyclosporine, and insulin.

37. The process of claim 30, wherein the fluid aqueous medium is selected from the group consisting of water, buffered water, phosphate buffered water, phosphate buffered saline,

citrate buffered water, acetate buffered water, water buffered with pharmaceutically acceptable pH controlling agents, water containing sodium chloride, water containing pharmaceutically acceptable salts, water containing soluble agents for lyoprotection, water containing soluble agents for cryoprotection, water containing dextrose, water containing mannitol, water containing trehalose, water containing sucrose, water containing sorbitol, water containing polyhydroxy-containing compounds, and a mixture thereof.

38. The process of claim 30, wherein the fluid aqueous medium is selected from the group consisting of a biological fluid, blood, plasma, saliva, urine, a protein-containing solution, an aqueous suspension of a protein, lymph fluid, semen, vaginal fluid, lachrymal fluid, nasal fluid, synovial fluid, cerebral fluid, cerebrospinal fluid, amniotic fluid, pancreatic fluid, pulmonary fluid, ascites fluid, fluid from a cyst, gastric fluid, intestinal fluid, a fluid removed from a patient, a diluted biological fluid, a concentrated biological fluid, and a mixture of biological fluids from one or more patients.

39. A composition comprising stable solid particles of itraconazole of a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

- a non-aqueous hydrophobic liquid in which itraconazole is not soluble or is poorly soluble, and is present in an amount such that the itraconazole remains insoluble in the non-aqueous hydrophobic liquid;

- a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

- a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substances that provides a self-dispersing property to said composition, wherein upon addition of said composition to a fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non-aqueous hydrophobic liquid containing particles of surface stabilized itraconazole suspended in the oily droplets of the dispersion and particles of said itraconazole migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

40. The composition of claim 39, wherein the non-aqueous hydrophobic liquid is selected such that itraconazole has a solubility of less than 25 mg/mL of the non-aqueous hydrophobic liquid.

41. The composition of claim 40, wherein the non-aqueous hydrophobic liquid is selected such that itraconazole has a solubility of from 0.02 to 16.0 mg/mL of the non-aqueous hydrophobic liquid.

42. The composition of claim 39, wherein the non-aqueous hydrophobic liquid is selected from the group consisting of decyl oleate, ethyl oleate, ethyl myristate, isopropyl myristate, ethyl caprate, MIGLYOL 840, soybean oil, MIGLYOL 810, capric triglyceride, ethyl alcohol, corn oil PEG-6 ester, propyleneglycol laurate, ethyl caprylate, MIGLYOL 818, apricot kernel oil, linoleic acid, PEG-200, PEG-300, PEG-400, triethyl citrate, MIGLYOL 812, glycerol triacetate, glycerol a,a'-diacetate, 1,2-propanediol, glycetyl linoleate, and Plurol oleique CC 497.

43. The composition of claim 42, wherein the non-aqueous hydrophobic liquid is selected from the group consisting of decyloleate, ethyl oleate, ethyl myristate, isopropyl myristate, ethyl caprate, MIGLYOL 840, soybean oil, MIGLYOL 810, capric triglyceride, corn oil PEG-6 ester, propyleneglycol laurate, ethyl caprylate, MIGLYOL 818, apricot kernel oil, linoleic acid, triethyl citrate, MIGLYOL 812, glycerol triacetate, glycerol a,a'-diacetate, 1,2-propanediol, glycetyl linoleate, and Plurol oleique CC 497.

44. The composition of claim 43, wherein the non-aqueous hydrophobic liquid is selected from the group consisting of decyloleate, ethyl oleate, ethyl myristate, isopropyl myristate, ethyl caprate, soybean oil, capric triglyceride, corn oil PEG-6 ester, propyleneglycol laurate, ethyl caprylate, apricot kernel oil, linoleic acid, triethyl citrate, glycerol triacetate, glycerol a,a'-diacetate, 1,2-propanediol, glycetyl linoleate, and Plurol oleique CC 497.

45. The composition of claim 39, wherein at least one surfactant component is selected from the group consisting of a natural or synthetic amphiphilic agent; a phospholipid; a nonionic surfactant; a polyoxyethylene fatty alcohol ether; a sorbitan fatty acid ester; a polyoxyethylene sorbitan fatty acid ester; glycerol triacetate; triacetin; a polyethylene glycol; cetyl alcohol; cetostearyl alcohol; stearyl alcohol; a poloxamer; a polaxamine; a polyoxethylene castor oil derivative; vitamin E; D-alpha-tocopheryl polyethylene glycol 1000 succinate; vitamin E TPGS; a PEG glyceryl fatty acid ester; PEG-8 glyceryl caprylate/caprate;

PEG-4 glyceryl caprylate/caprate; PEG-32 glyceryl laurate; PEG-6 glyceryl mono oleate; PEG-6 glyceryl linoleate; a propylene glycol mono fatty acid ester; a propylene glycol di-fatty acid ester; propylene glycol laurate; propylene glycol caprylate/caprate; diethylene glycol monoethyl ether; transcutol; a monoglyceride; an acetylated monoglyceride; glycerol monooleate; glycerol monostearate; a mono-acetylated monoglyceride; a di-acetylated monoglyceride; monoacetin; diacetin; an anionic surfactant; a fatty acid salt; a bile salt; potassium laurate; triethanolamine stearate; sodium lauryl sulfate; an alkyl polyoxyethylene sulfate; sodium alginate; dioctyl sodium sulfosuccinate; sodium carboxymethylcellulose; calcium carboxymethylcellulose; a cationic surfactant; a pharmaceutically acceptable quaternary ammonium compound; benzalkonium chloride; cetyltrimethylammonium bromide; lauryldimethylbenzylammonium chloride; polyethylene glycol; PEG 1000; PEG 1500; and PEG 3400.

46. The composition of claim 45, wherein the phospholipid is selected from the group consisting of a saturated phospholipid, an unsaturated phospholipid, a synthetic phospholipid, a natural phospholipid, and a combination thereof.

47. The composition of claim 39, wherein at least one hydrophilic component is selected from the group consisting of a low-molecular weight monohydric alcohol; a low-molecular weight polyhydric alcohol; ethanol; a glycol; glycerol; and a mixture thereof.

48. The composition of claim 39, in a dosage form for peroral, parenteral, transdermal, inhalation, or ophthalmic administration of said biologically active substance.

49. A process for preparing a dosage form of itraconazole comprising adding to a fluid aqueous medium a composition comprising stable solid particles of itraconazole having a volume weighted mean particle size in the range of 0.01 to 10 micrometers, which particles are dispersed in a non-aqueous carrier system comprised of:

a non-aqueous hydrophobic liquid in which said itraconazole is not soluble or is poorly soluble, and is present in an amount such that the itraconazole remains insoluble in the non-aqueous hydrophobic liquid;

a surfactant system consisting of at least one surfactant which is soluble in said non-aqueous hydrophobic liquid, wherein at least a portion of which surfactant system absorbs to the surface of said particles; and

a quantity of not more than about 10% of the total weight of said composition of one or more hydrophilic substances that provides a self-dispersing property to said composition, wherein upon addition of said composition to a fluid aqueous medium, said composition self-disperses in said fluid aqueous medium to form a suspension comprising droplets of non aqueous hydrophobic liquid containing particles of surface stabilized itraconazole suspended in the oily droplets of the dispersion and particles of said itraconazole migrated into said fluid aqueous medium wherein said particles have a size in the range of 0.01 to 10 micrometers and have associated therewith on the surface at least a portion of said surfactant system.

50. The process of claim 49, wherein the non-aqueous hydrophobic liquid is selected such itraconazole has a solubility of less than 25 mg/mL of the non-aqueous hydrophobic liquid.

51. The process of claim 50, wherein the non-aqueous hydrophobic liquid is selected such itraconazole has a solubility of from 0.02 to 16.0 mg/mL of the non-aqueous hydrophobic liquid.

52. The process of claim 40, wherein the non-aqueous hydrophobic liquid is selected from the group consisting of decyl oleate, ethyl oleate, ethyl myristate, isopropyl myristate, ethyl caprate, MIGLYOL 840, soybean oil, MIGLYOL 810, capric triglyceride, ~~ethyl alcohol~~, corn oil PEG-6 ester, propyleneglycol laurate, ethyl caprylate, MIGLYOL 818, apricot kernel oil, linoleic acid, PEG-200, PEG-300, PEG-400, triethyl citrate, MIGLYOL 812, glycerol triacetate, glycerol a,a'-diacetate, 1,2-propanediol, glyceryl linoleate, and Plurol oleique CC 497.

53. The process of claim 52, wherein the non-aqueous hydrophobic liquid is selected from the group consisting of decyloleate, ethyl oleate, ethyl myristate, isopropyl myristate, ethyl caprate, MIGLYOL 840, soybean oil, MIGLYOL 810, capric triglyceride, corn oil PEG-6 ester, propyleneglycol laurate, ethyl caprylate, MIGLYOL 818, apricot kernel oil, linoleic acid, triethyl citrate, MIGLYOL 812, glycerol triacetate, glycerol a,a'-diacetate, 1,2-propanediol, glyceryl linoleate, and Plurol oleique CC 497.

54. The process of claim 53, wherein the non-aqueous hydrophobic liquid is selected from the group consisting of decyloleate, ethyl oleate, ethyl myristate, isopropyl myristate, ethyl caprate, soybean oil, capric triglyceride, corn oil PEG-6 ester, propyleneglycol laurate, ethyl

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caprylate, apricot kernel oil, linoleic acid, triethyl citrate, glycerol triacetate, glycerol a,a'-diacetate, 1,2-propanediol, glyceryl linoleate, and Plurol oleique CC 497.